## REMARKS

Claims 56, 72, 73, 75 and 76 are pending and stand rejected. Claims 1-3, 5-8, 10, 13, 77 and 78 stand withdrawn.

In light of the following remarks, Applicants respectfully request reconsideration and allowance of claims 56, 72, 73, 75 and 76.

Information Disclosure Statements

The Examiner stated that certain references listed on the Information Disclosure Statements previously filed in the instant application were not considered, either because they were not submitted or because they were not in English.

Applicants resubmit herewith the references that were not considered by the Examiner.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 56, 72, 73, 75 and 76 under 35 U.S.C. § 103(a), alleging that they are unpatentable over EP 0605963 ("Wright") in view of U.S. Patent No. 5,824,778 ("Ishikawa"), in view of the Rotondaro et al. publication (*Mol. Biotechnol.* (1999) 11:117-128; "Rotondaro"), in view of U.S. Patent No. 6,083,909 ("Sommermeyer"), in view of the Peluso et al. publication (*Tetrahedron Lett.* (2001) 42:2085-2087; "Peluso"), in view of PCT Publication No. WO 80/02374 ("Berger"). The Examiner asserted that Wright teaches methods and compounds for chemically modifying proteins and other similar organic molecules by covalent conjugation to water-soluble organic polymers, such as polyethylene glycol (PEG), which can confer desirable properties to the proteins. The Examiner asserted that Wright also teaches that it may be advantageous to couple water-soluble reagents to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids, and that hydrazine and oxylamine derivatives of water-soluble polymers may be covalently attached to proteins through reactions with aldehyde groups or other suitable functional groups that are present on the protein of interest or are introduced by partially oxidizing the hydroxyl groups on the polypeptide.

The Examiner acknowledged that Wright does not expressly teach conjugation of water soluble polymer to a polypeptide via a hydrazone or oxime linkage wherein the polypeptide is G-

CSF, nor does Wright teach conjugation of G-CSF to HES. The examiner asserted, however, that:

(1) Ishikawa discloses a PEG-modified human G-CSF, where the PEG is covalently bound to amino acid residues of the G-CSF (e.g., amino acids having a free amino group or a free carboxyl group);

(2) Rotondaro discloses purification and characterization of two recombinant human G-CSF glycoforms expressed from an engineered CHO cell line;

(3) Sommermeyer teaches conjugates in which hemoglobin and HES are linked to one another selectively via amide bonds between free amino groups of the hemoglobin and the reducing end group of the HES, which is present in oxidized form;

(4) Peluso teaches chemoselective ligation for the assembly of N-linked glycopeptide mimetics; and

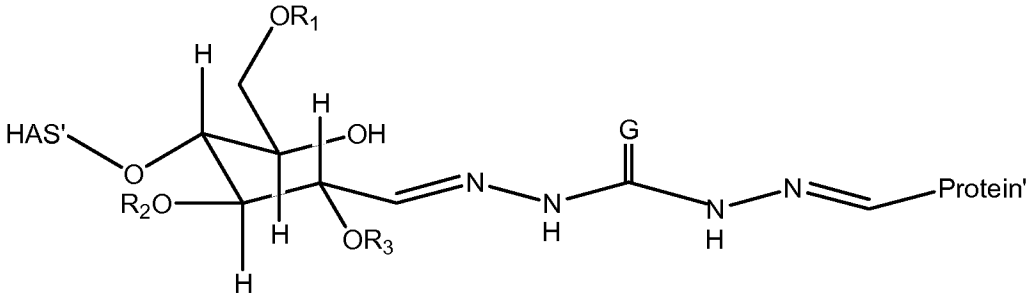
(5) Berger teaches a composition for the controlled release administration of a biologically active compound, comprising a combination of the biologically active compound and HAS, preferably HES.

Taking all of these disclosures into account, the Examiner alleged that it would have been obvious at the time of the invention to combine the teachings of these six references. The Examiner further alleged that although Wright does not expressly teach the position on the starch at which conjugation of the polypeptide via hydrazine and hydroxylamine linkers should occur, it is known from the prior art that polypeptides can be conjugated to the reducing end sugar of starch as in Sommermeyer and also in Peluso, which teaches that hydrazides can be chemo-selectively ligated to a reducing end carbohydrate residue. Thus, concluded the Examiner, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

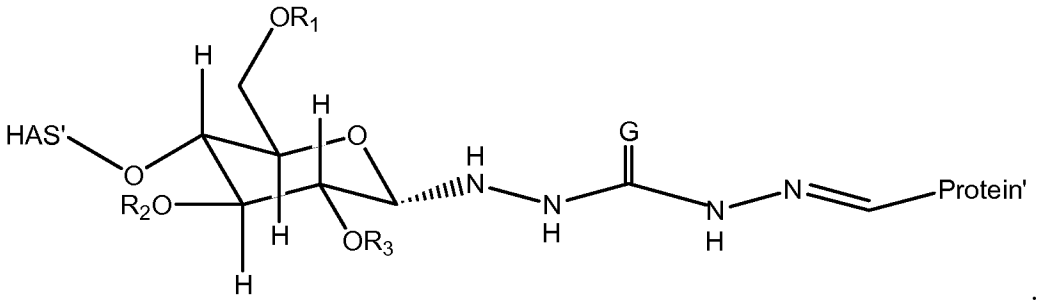
Applicants respectfully disagree. The present claims recite a chemical composition. As the Federal Circuit clarified in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1363 (Fed. Cir. 2007), and *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008), in order to establish that a chemical compound is obvious over a compound in the prior art, one must: 1) identify a starting reference point or points in the art (i.e., a lead compound), prior to the time of invention, from which a skilled artisan might identify a problem and pursue a potential solution; 2) identify some reason, available within the knowledge

of one of skill in the art, to make the *specific molecular modifications* necessary to result in the claimed compound; and 3) identify " some reasons for narrowing the prior art universe to a finite number of identified, predictable solutions." *See*, *Eisai*, 533 F.3d at 1359. Importantly, in an unpredictable art such as chemistry, *Eisai* confirmed that a focus on "identified, predictable solutions" may present a difficult hurdle because of the genuine unpredictability of the art. *Id.*

In the present case, the Examiner has not identified any particular lead compound, nor identified a problem to be solved based on the molecules disclosed in the cited references. Importantly, the Examiner also has not identified a reason to make the *specific molecular modifications* required to alter any lead compound in the cited references to result in the conjugates specifically claimed in the present application. For example, the Examiner has failed to identify a reason for modifying the prior art universe of polymer-protein conjugates to the presently recited conjugates in which HAS is coupled to G-CSF via a bifunctional carbohydrazide linker, where the linker is selectively coupled to the non-oxidized reducing end of the HAS and to a carbonyl group of G-CSF, such that the conjugate has a structure according to the formula




and/or




In addition, the Examiner has not set forth any rationale why modified versions of any of the conjugates described in the cited references would represent identified, predictable solutions to

any identified problem of a lead molecule disclosed therein. Accordingly, Applicants respectfully submit that the Examiner's burden of showing that a skilled artisan would have been rationally and logically prompted to modify the prior art chemistries to result in the specifically claimed conjugates has not been met.

Further, Applicants submit that the combined teachings of the cited references do not suggest a HAS-G-CSF conjugate as recited in the present claims. First, Wright teaches coupling bifunctional linker molecules to PEG by functionalizing hydroxyl or amino groups of the PEG with the linker compound. *See*, e.g., the examples for synthesis of hydrazone forming m-PEG at pages 12-14. For example, formula (III) at page 7 of Wright depicts a hydrazine derivative of a water-soluble organic polymer (P), such as PEG, in which an amino group is functionalized with a carbonic acid hydrazide. *See*, also, page 13, line 51 to page 14, line 16, which disclose the synthesis of mPEG-semicarbazide from mPEG5000-amine using hydrazine, phosgene and triethylamine. Such functionalization is non-specific and, in the case of a polysaccharide having various hydroxyl functions (e.g., HES), would mandatorily yield mixtures of polymers being statistically and unselectively functionalized with the linker compound at various positions.

Thus, as acknowledged by the Examiner, Wright does not teach or suggest selective functionalization of a polysaccharide via its reducing end (thus via an aldehyde or hemiacetal group of a polymer), much less chemoselective coupling of a hydrazide comprising linker to the reducing end.

Since Wright contains no teaching regarding functionalization of a polymer via groups other than hydroxyl groups or amino groups, a person skilled in the art, starting from Wright (e.g., from the "leading compound" having the structure according to formula (VI) as set forth at page 7) would have had no reason to modify the compounds taught by Wright and to prepare a compound by coupling a linker selectively to the non-oxidized reducing end of a polysaccharide – in other words by linking a polymer via an aldehyde or hemiacetal group present in the polymer to a protein using a bifunctional linker.

Thus, in summary, Wright does not teach:

• selective functionalization of a polysaccharide via its reducing end, much less via the non-oxidized reducing end;

• coupling of a homobifunctional carbohydrazide linker to the reducing end; or

• selective coupling of such a linker to a carbonyl group of G-CSF.

None of the other cited references cited remedies the deficiencies of Wright, as described below.

Ishikawa discloses a biologically active G-CSF-PEG conjugate, wherein the PEG polymer is covalently attached to at least one amino acid of the G-CSF polypeptide via a free amino or carboxyl group present in the polypeptide (*see*, e.g., column 2, line 66 to column 3, line 8). Ishikawa contains no suggestion that G-CSF should be coupled to PEG via a carbonyl group present in the glycoprotein, let alone any coupling via a carbonyl group using a bifunctional carbohydrazide linker. Further, Ishikawa contains no suggestion that polysaccharides should be coupled to other molecules via their reducing end.

Thus, like Wright, Ishikawa also does not teach selective functionalization of a polysaccharide via its reducing end, much less via its non-oxidized reducing end, coupling a homobifunctional carbohydrazide linker to the reducing end of a polysaccharide, or selective coupling of such a linker to a carbonyl group of G-CSF. Accordingly, Ishikawa does not remedy the deficiencies of Wright.

Rotondaro discloses a specific glycoform of G-CSF, and is completely silent with regard to conjugates between G-CSF and polysaccharides, with or without a linker. Thus, Rotondaro does not remedy the deficiencies of Wright and Ishikawa.

Sommermeyer relates to hemoglobin-hydroxyethylstarch (HES) conjugates in which hemoglobin and HES are selectively coupled to one another via free amino groups of the hemoglobin and the oxidized reducing end group of the HES. *See*, for example, column 3, lines 39-45, column 5, lines 63-67, and column 6, lines 5-9. Accordingly, in the conjugate taught in Sommermeyer, the protein is directly attached via an amide bond to the oxidized reducing end of HES. Sommermeyer does not teach or suggest any conjugate in which a HAS moiety is linked via an imine bond (in the open sugar form) or an amine bond (in the closed sugar form), respectively, to a hydrazide linker compound, wherein the linker compound in turn is attached to the protein via an imine bond. Accordingly, Sommermeyer does not remedy the deficiencies of Wright, Ishikawa, and Rotondaro.

Peluso does not remedy the deficiencies of the combination of above-mentioned references. In particular, Peluso only discloses the coupling of an unnatural tripeptide to a

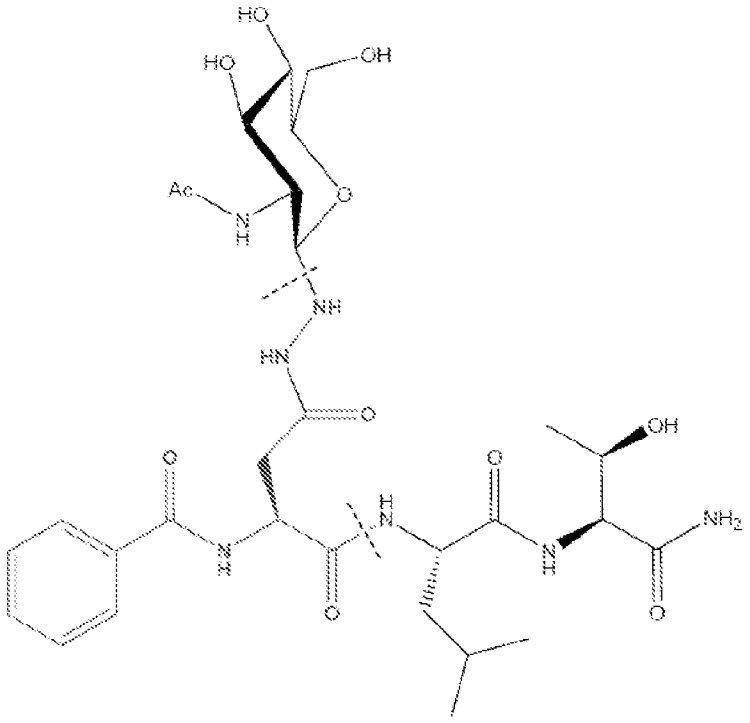
monosaccharide via a hydrazide group. Peluso discloses no conjugate comprising either a protein or a polysaccharide.

Since the chemistry and, in particular, the reaction behavior of large molecules such as polysaccharides and polypeptides is significantly different from the reaction behavior of monosaccharides and small peptides, any teaching regarding the synthesis of conjugates comprising monosaccharides and small oligopeptides can not necessarily be transferred to large polysaccharides and polypeptides. Thus, Applicants submit that a skilled person starting with Wright and searching for advantageous new conjugates between polysaccharides and proteins, such as G-CSF, would not have taken the teaching of Peluso into account.

Applicants further submit that even if such a skilled person would have taken Peluso into account, s/he would not have arrived at the presently claimed conjugates. In this respect, Applicants note that the conjugate taught by Peluso contains no bifunctional linker compound. Instead, the hydrazide group present in the tripeptide according to Peluso was introduced during synthesis of the tripeptide itself, using an unnatural amino acid. Thus, the hydrazide group was not introduced by attaching a linker to an existing peptide, much less by attaching a bifunctional carbohydrazide linking compound to an aldehyde group of a peptide (or polypeptide) to form an imine group between the aldehyde group and the linking compound.

Thus, Peluso does not teach or suggest a conjugate between a polysaccharide and a protein in which a bifunctional linking compound, in particular a homobifunctional carbohydrazide linker, links both compounds.

In case the Examiner considers the unnatural amino acid alanine-β-hydrazide (the portion of the structure below between the dashed lines) to be a linker molecule connecting a dipeptide to a saccharide, Applicants submit that Peluso in combination with the other cited documents still does not suggest the specific conjugate claimed. This is particularly true given that the alanine-β-hydrazide moiety only "links" the N-terminus of a dipeptide to a saccharide, rather than linking a saccharide to an aldehyde group of a peptide. No linkage via an aldehyde group or hemiacetal group of a peptide, much less a protein, is suggested.




Accordingly, Peluso does not remedy the deficiencies of Wright combined with Ishikawa, Rotondaro, and Sommermeyer.

Berger discloses coupling biologically active components to polymers using non-selective methods. In particular, Berger discloses modification of HES using cyanogen bromide, as set forth in scheme 1 at page 7. Berger fails to suggest conjugates involving selective coupling via the reducing end of HES. Consequently, Berger does not remedy the deficiencies of Wright when combined with the other cited references.

In summary, a person of ordinary skill in the art at the time of Applicants' priority date, reading Wright in combination with any or all of the other cited references, would not have found it obvious to make a conjugate as recited in present claim 56, in which a bifunctional carbohydrazide linker is chemoselectively coupled to the non-oxidized reducing end of HAS and further to an aldehyde group of a polypeptide. Accordingly, the present claims are patentable over the cited combination of references.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 56, 72, 73, 75 and 76 under 35 U.S.C. § 103(a).

Double Patenting

The Examiner provisionally rejected claims 56, 72, 73, 75 and 76 under the judicially created doctrine of obviousness-type double patenting, alleging that they are unpatentable over claims 1-3, 7, 8, 10 and 14 of copending application no. 11/518,558, in view of Ishikawa, for reasons of record. Applicants note that the 11/518,558 application has now issued as U.S. Patent No. 8,017,739.

The Examiner also provisionally rejected claims 56, 72, 73, 75 and 76 under the judicially created doctrine of obviousness-type double patenting, alleging that they are unpatentable over claims 60 and 61 of copending application no. 12/824,618, in view of Wright, in view of Ishikawa, for reasons of record.

In addition, the Examiner provisionally rejected claims 56, 72, 73, 75 and 76 under the judicially created doctrine of obviousness-type double patenting, alleging that they are unpatentable over claims 1-6, 9, 17-20, 27 and 29 of copending application no. 13/018,648, in view of Ishikawa, for reasons of record.

Applicants respectfully request that these rejections be held in abeyance until the Examiner considers the claims to be otherwise in condition for allowance.

## CONCLUSION

Applicants submit that claims 56, 72, 73, 75, and 76 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $1110 for the Petition for Extension of Time fee, and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date: September 21, 2011

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